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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/147,947	03/24/99	TSURUOKA N	001560-349

021839
BURNS DOANE SWECKER & MATHIS L L P
POST OFFICE BOX 1404
ALEXANDRIA VA 22313-1404

HM22/0912

EXAMINER	
MOORE,W	
ART UNIT	**PAPER NUMBER**
1652	11

DATE MAILED: 09/12/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/147,947	Applicant(s) TSURUOKA ET AL.	
	Examiner William W. Moore	Art Unit 1652	

-- Th MAILING DATE of this communication app ars on th c ver sh t with th correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

1)☒ Responsive to communication(s) filed on *10 January 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *10 and 17-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9 , 11-16 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☒ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☒ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

Information Disclosure Statement

Applicants' submission of an Information Disclosure Statement, Paper No. 4 filed June 28, 1999, is hereby acknowledged.

Specification

Applicants' preliminary Amendment A filed with the specification on March 24, 1999, has been entered, amending claims 5-7, 10 and 11 and introducing the new claims 12-17. Applicants' preliminary Amendments B and C filed, respectively, November 1, 1999 and January 10, 2000, have been entered, amending both the printed and the computer-readable forms of the sequence listing. In response to this communication, an amendment to page 1, line 5, of the specification must be submitted that identifies both Applicants' PCT and national priority documents. Receipt is acknowledged of papers submitted under 35 U.S.C. §119, which papers have been placed of record in the file. A Notice of Draftsman's Patent Drawing Review, stating informalities requiring correction, accompanies this communication.

Election/Restrictions

Restriction is required under 35 U.S.C. §§121 and 372. This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In accordance with 37 CFR 1.499, applicant is required, in response to this action, to elect a single invention to which the claims must be restricted.

I. Claims 1-4 and 11, drawn to a first product, a human serine protease and its component domains, and to a first use of that product in screening for "physiologically active substance", classified in Class 435, subclass 226.

II. Claims 5-9 and 12-16, drawn to a second product, a DNA encoding a human serine protease or its component domains, to vectors and transformed host cells comprising said DNA, and to a first method of use of that product in a recombinant method of making a protease, classified in Class 536, subclass 23.2.

III. Claims 10 and 17-19, drawn to a third product, an antibody capable of recognizing a human serine protease. classified in Class 530, subclass 387.1.

IV. Claim 20, drawn to a second method of use of the second product in screening for physiologically active substances, classified in Class 435, subclass 6.

The inventions are distinct, each from the other, because of the following reasons:

Inventions of Group I and Group II are related as process of making and product made. The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make other and materially different products, or, (2) that the product as claimed can be made by another and materially different process (MPEP §806.05(f)). In the instant case the protease product of Group I may also be made by another and materially different process such as solid-phase chemical synthesis.

Inventions of Group I and Group III are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP §806.04, MPEP §808.01). In the instant case the different inventions have different modes of operation, different functions, and different effects.

Inventions of Group I and Group IV are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP §806.04, MPEP §808.01). In the instant case the different inventions have different modes of operation and different functions.

Inventions of Group II and Group III are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP §806.04, MPEP §808.01). In the instant case the different inventions have different modes of operation, different functions, and different effects.

Inventions of Group II and Group IV are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP §806.05(h)). In the instant case the product as claimed can be used in a materially different process of using that product such as the recombinant production of a protease.

Inventions of Group III and Group IV are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP §806.04, MPEP §808.01). In the instant case the different inventions have different modes of operation and different functions.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification restriction for examination purposes as indicated is proper.

During a telephone conversation with Ms. Dawn M. Gardner on July 24, 2000, a provisional election was made **with** traverse to prosecute the invention of Group I, claims 1-4 and 11. Affirmation of this election must be made by applicant in responding to this Office action. Because a prior art search for the subject matters of Group I also revealed corresponding subject matters of Groups II and IV, the restriction requirement between these three Groups is hereby rescinded and claims 1-9, 11-16 and 20 are examined herein. Claims 10 and 17-19 are withdrawn from further consideration by the Examiner, 37 CFR §1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR §1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 CFR §1.48(b) and by the fee required under 37 CFR §1.17(h).

35 U.S.C. §101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.

Claims 1-6 and 9 are rejected under 35 U.S.C. §101 because the claimed invention is directed to non-statutory subject matter.

Naturally-occurring compositions of matter are not statutory subject matter and the claims must distinguish a composition of matter which might otherwise be present in Nature by indicating its removal from Nature. Amendments to these claims that adopt recitations describing, in claim 1, "an **isolated** serine protease", in claim 2, "an **isolated**

serine protease domain", in claim 4, "an **isolated** kringle", in claim 4, "an **isolated** scavenger receptor cysteine-rich domain", and in claims 5 and 6, "an isolated DNA", will overcome this aspect of the rejection.

Claim 9 describes impermissible subject matter in reciting "breeding a host" because it does not exclude persons who may not, under the 14th Amendment to the Constitution, be subjected to involuntary servitude. Non-consensual recovery of expressed neurotrypsin from a person may also violate criminal and civil law in the United States.

Claim Rejections - 35 USC § 112

Claim 1-9 and 11-16 are rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for the preparation of a human neurotrypsin/BSSP of claim 1 **consisting of** the amino acid sequence of SEQ ID NO:6 and a nucleotide sequence that encodes it, and for the preparation of a functioning serine protease domain of a human neurotrypsin/BSSP of claim 2 **comprising** the amino acid sequence region from position 578 to position 822, inclusive, of SEQ ID NO:6 and a nucleotide sequence that encodes it, the preparation of an active kringle domain of a human neurotrypsin/BSSP of claim 3 **comprising** the amino acid sequence region from position 40 to position 112, inclusive, of SEQ ID NO:6 and a nucleotide sequence that encodes it, the preparation of a functioning scavenger receptor cysteine-rich domain of a human neurotrypsin/BSSP of claim 4 **comprising an amino acid sequence region selected from the group of regions consisting of** position 117 to position 217, inclusive, of SEQ ID NO:6 and a nucleotide sequence that encodes it, position 227 to position 327, inclusive, of SEQ ID NO:6 and a nucleotide sequence that encodes it, position 334-433, inclusive, of SEQ ID NO:6 and a nucleotide sequence that encodes it, and position 447 to position 547, inclusive, of SEQ ID NO:6 and a nucleotide sequence that encodes it, as well as for the use of the human neurotrypsin/BSSP of SEQ ID NO:6 of claim 1, and a nucleotide sequence that encodes it of claim 13, in processes for screening physiologically active substances that has some certain, recognizable, result,

does not reasonably provide enablement for the myriad of partial peptides of each of the native human neurotrypsin/BSSP and its various domains wherein unspecified portions are altered by undescribed amino acid sequence substitutions, deletions and/or additions. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

It is noted at the outset that a discussion of the enablement problems presented by the claims as filed might be better focussed if Applicants' intended subject matters were clearly and definitely described. Taken in its best light, the current state of claims 1-4 suggests that Applicants contemplate arbitrary assignments of any number of amino acid deletions or substitutions in the overall neurotrypsin amino acid sequence and certain of its domains,

as well as arbitrary assignments of amino acid additions in the overall neurotrypsin amino acid sequence and those same domains. The specification does not support introduction of random amino acid insertions, deletions, or substitutions anywhere, in any combination or any pattern, in the native serine protease of SEQ ID NO:6 or its separate domains and, indeed, describes no specific locations for substitutions, deletions or insertions anywhere in the amino acid sequence of SEQ ID NO:6, nor does it describe any substituents. Neither the prior art made of record herewith nor Applicant's specification can identify a single amino acid in the primary sequence of this or any other human serine protease that might be altered, nor teach the nature of an alteration that may be made, which permits a resulting polypeptide to function as a serine protease, a kringle domain or a scavenger receptor cysteine-rich domain. The prior art made of record herewith is evidence that no teaching in the relevant arts of protein engineering and molecular biology can be combined with the disclosure of the instant specification to support such extensive alteration. **See**, e.g., Bott et al., U.S. Patent No. 5,700,676, made of record herewith, who were able to concurrently alter no more than 4% of the amino acid positions in a secreted prokaryotic protease, the three-dimensional structure of which had already been determined by X-ray diffraction analysis. Mere sequence perturbation will not enable the design and preparation of nucleotide sequences encoding a myriad of divergent polypeptides and provide the public with a nucleotide sequence encoding a product that retains a recognizable function.

Claims 8 and 9 present an additional issue of enablement because both embrace intact animals, as well as individual cells, as hosts for an expression vector maintaining a DNA encoding, at least, a human neurotrypsin. While it is agreed that both prokaryotic and eukaryotic **host cells**, including vertebrate cells in culture, may be transformed or transfected with an expression vector maintaining a DNA encoding a human neurotrypsin, the specification provides no guidance whatsoever for production of a transgenic animal

that expresses a transforming, human neurotrypsin-encoding DNA, and such expression is not supported in the art as evidenced by the prior art made of record herein. Undue experimentation would be required on the part of an artisan to determine how to convey a transforming DNA to, e.g., central nervous system tissue for its successful expression.

It is well settled that 35 U.S.C. §112, first paragraph, requires that a disclosure be sufficiently enabling to allow one of skill in the art to practice the invention as claimed without undue experimentation and that unpredictability in an attempt to practice a claimed invention is a significant factor supporting a rejection under 35 U.S.C. §112, first paragraph, for non-enablement. See, *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (recognizing and applying the "Forman" factors). Cf., *Ex parte Forman*, 230 USPQ 546, 547 (Bd. Pat. App. & Int. 1986) (citing eight factors relevant to analysis of enablement). The standard set by the CCPA, the predecessor of the present Court of Appeals for the Federal Circuit, is not to "make and screen" any and all possible alterations because a reasonable correlation must exist between the scope of guidance provided by the specification and the scope asserted in the claimed subject matter. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 25 (CCPA 1970) (scope of enablement varies inversely with the degree of unpredictability of factors involved in physiological activity of small peptide hormone); see also, *Ex parte Maizel*, 27 USPQ2d 1662, 1665 (Bd. Pat. App. & Int. 1992) (functional equivalency of divergent gene products not supported by disclosure only of a single B-cell growth factor allele). The standard set by the CCPA was approved by the Federal Circuit in *Genentech, Inc. v. Novo-Nordisk A/S*, 42 USPQ2d 1001 (Fed. Cir. 1997). An appellate panel recently considered whether definitional statements might enable a claim scope argued to extend beyond a disclosed, recombinantly-produced, gene product having its native amino acid sequence to embrace a specific variant gene product encoded by a specifically-altered DNA sequence. *Genentech, Inc. v. The Wellcome*

Found. Ltd., 29 F.3d 1555, 31 USPQ2d 1161 (Fed. Cir. 1994). The court held that only a narrow structural and functional definition was enabling precisely because the sweeping definitions of scope in the patent specification could not reasonably have been relied upon by the PTO in issuing the patent. *Genentech*, 29 F.3d 15 at 1564-65, 31 USPQ2d at 1168. Applying the "*Forman*" factors discussed in *Wands*, supra, to Applicant's disclosure, it is apparent that:

a) the specification lacks adequate, specific, guidance for altering DNA sequences encoding human neurotrypsin, its domains, or the encoded amino acid sequences,

b) the specification lacks working examples wherein human neurotrypsin-encoding regions of the DNA sequence, and the encoded neurotrypsin, are altered,

c) in view of the prior art publications of record herein, the state of the art and level of skill in the art do not support such alteration, and,

d) unpredictability exists in the art where no functional regions of mammalian neurotrypsins have been specifically altered, yet retained their biological function.

Thus subject matters embraced by claims 1-4, and by virtue of their dependency thereon, claims 5-9, 11-16 and 20 are considered to have a scope unsupported by Applicants' specification, even when taken in combination with the teachings available in the prior art. Limitation of the subject matters as indicated in the paragraph spanning pages 4 and 5 above is required in order to overcome this rejection. It is noted that amendments so limiting claims 1-4 will avoid the prior art cited hereinbelow and may assist Applicants in overcoming the following rejection under the second paragraph of the statute.

Claims 1-6, 9, 11, 13 and 20 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In addition to initially identifying an intact human neurotrypsin protease or a specific, intact, domain, of each of claims 1-4 then counterposes "its partial peptide comprising an amino acid sequence identical" to the intact protease or domain against a terminal clause reciting "an amino acid sequence in which a portion of the identical amino acid sequence is deleted". This renders the claims indefinite because a partial peptide is already a deletion

of the intact amino acid sequence and each claim seems to attempt to describe it twice. This ambiguity is compounded by an intermediate clause reciting 'an amino acid sequence in which a portion of the identical", considered to refer to the intact, "amino acid sequence is deleted or substituted" thus describing both internal truncations and terminal truncations, the latter of which will result in "its partial peptide". There is no resolution proposed to these ambiguities because the subject matter alternative to an intact protease, or an intact domain, that Applicants intended to describe is uncertain. Accordingly, prior art cited as anticipatory in the further rejections below is applied to both claims 5 and 6 in the same rejection where a DNA of claim 5 which encodes a protease, a domain, or a partial peptide that varies by the confusing array of amino acid sequence modifications is also a DNA of claim 6 that hybridizes to a DNA encoding the naturally-occurring human neurotrypsin.

Claims 1-4 are each seen to describe, in their variegated, full-length, protease and its domains, a broad range or limitation together with a narrow range or limitation, in their variegated partial peptides, that falls within the broad range or limitation in the same claim thus are indefinite since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See, *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), wherein broad language followed by "such as" and then narrow language was held to render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. See also, *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). If Applicants desire to claim the various peptides described by the lesser included recitations of scope in

each of the rejected claims, patent prosecution in this national forum requires that further, dependent, claims separately reciting an additional limitation of scope be presented.

Claims 5, 6 and 9 are further indefinite in reciting "serine protease, domain or their partial peptide(s)". Claim 5 recites the phrase once and claims 6 and 9 recite it twice. It is apparently an artefact or a miss-translation. It is not clear - and the single comma in the phrase makes it less clear - what Applicants intend a DNA to encode where claim 1, from which claims 5, 6 and 9 ultimately depend, recites no "domain". Again no resolution to this ambiguity can be proposed because the subject matter alternative to an intact protease and a "partial peptide(s), that Applicants might have intended to describe is uncertain.

Claims 11, 13 and 20 are rejected because they state neither a purpose nor a process step and because their grammar is defective. Both deficiencies render the claims indefinite. Recitations of a "process for screening . . . that uses the serine protease, domain or . . . partial peptide" in claim 11, and in claims 13 and 20 a "process for screening . . . that uses the DNA", are indefinite because they are meaningless where no physiological role or characteristic for a physiologically active substance is indicated. Ions, solvents, and all classes of organic compounds are "physiologically active" substances and any of these might conceivably affect a human neurotrypsin or a nucleic acid. What is the physiological activity Applicants are screening in substances? The processes that Applicants might have intended are unclear where the claims set forth no process steps. Claims are also indefinite in merely reciting a use without any active, positive steps indicating how the use is actually practiced thus claims 11, 13 and 20 constitute omnibus type claims in failing to point out what is included or excluded by the claim language. This aspect of the rejection may be overcome by, e.g., amending the claims to include process steps. In addition, the word "substance" in claims 11, 13 and 20 should be in the plural since the indefinite article "a" - which would invoke the singular - does not occur before "physiologically active".

Claim Rejections - 35 USC §§102 and 103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. §102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1-4 embrace many prior art disclosures due to their broad, ambiguous, scope. The closest prior art has been selected for application in the following rejections.

Claims 1-6, 13 and 20 are rejected under 35 U.S.C. §102(a) as being anticipated by Gschwend et al., **Molecular and Cellular Neuroscience**, Vol. 9, pages 207-219, published July 23, 1997, a day in advance of Applicants' foreign priority date. Gschwend et al. disclose, see Figure 2A at page 210, the amino acid sequence and encoding DNA sequence of the murine neurotrypsin, the same amino acid sequence as that set forth in SEQ ID NO: 4 herein. The murine neurotrypsin anticipates the claimed subject matter because it has 66.4% sequence similarity with the amino acid sequence of the human neurotrypsin set forth in SEQ ID NO:6 herein and comprises extensive partial peptides differing by only a few amino acid substitutions, deletions, and/or additions from the human neurotrypsin of SEQ ID NO:6 and claim 1 and from the domains indicated in claims 2, 3, and 4. Claims 5 and 6 are included in this rejection due to their ambiguity as the DNA sequence of Gschwend et al. meets limitations of both. Figure 6 of Gschwend et al. anticipates claims 13 and 20 because mRNA is physiologically active.

Claims 2, 6, 12 and 14 are rejected under 35 U.S.C. §102(e) as being anticipated by Au-Young et al., U.S. Patent No. 5,869,637, available as prior art by virtue of its July 22, 1996, filing date who disclose the amino acid sequence of a human kallikrein, a serine protease, SEQ ID NO:1, and its encoding DNA, SEQ ID NO:2. The protease of Au-Young et al. shares 39% amino acid sequence similarity with the human neurotrypsin protease domain present in SEQ ID NO:6 herein and comprises extensive partial peptides differing by "at least one" amino acid substitution, deletion, and/or addition from the human neurotrypsin protease domain of SEQ ID NO:6 and claim 2. Au-Young et al. further disclose, cols. 8-12, the preparation of an expression vector comprising a DNA encoding the human kallikrein protease and of a host cell transformed with the expression vector.

Claims 2, 6, 12 and 14 are rejected under 35 U.S.C. §102(b) as being anticipated by Fujikawa et al., **Biochemistry**, Vol. 25, pages 2417-2424, who disclose the human blood coagulation factor XI, a serine protease, and its encoding DNA, see Figure 2. The protease domain of human factor XI shares 33% amino acid sequence similarity with the protease domain of human neurotrypsin set forth in SEQ ID NO:6 herein and comprises extensive partial peptides that differ by "at least one" amino acid substitution, deletion, and/or addition from the human neurotrypsin protease domain of claim 2. Fujikawa et al. further disclose, pages 2418-2420, preparation of an expression vector comprising DNA encoding the human factor XI protease and of a host cell transformed with the vector.

Claim 3, 6, 12 and 15 are rejected under 35 U.S.C. §102(b) as being anticipated by Wood et al., WO 96/03644, who disclose the human mlk receptor tyrosine kinase, SEQ ID NO:2 and its encoding DNA, SEQ ID NO:1. The human mlk receptor tyrosine kinase kringle domain shares 34% amino acid sequence similarity with the kringle domain of human neurotrypsin set forth in SEQ ID NO:6 herein and comprises extensive partial

peptides differing by "at least one" amino acid substitution, deletion, and/or addition from the human neurotrypsin kringle domain of claim 3. Wood et al. further disclose, pages 34-39, the preparation of expression vectors comprising DNAs encoding human and murine mlk receptor kinases, and of host cells transformed with the expression vectors, for recombinant production of both human and murine enzymes.

Claims 3, 6, 12 and 15 are rejected under 35 U.S.C. §102(e) as being anticipated by Anderson et al., U.S. Patent No. 5,714,145, who disclose the human serine protease tissue plasminogen activator [tPA], see Figure 2, and inherently disclose an encoding DNA sequence. The kringle-2 domain of human tPA shares 32% amino acid sequence similarity with the kringle domain of human neurotrypsin set forth in SEQ ID NO:6 herein and comprises extensive partial peptides that differ by "at least one" amino acid substitution, deletion, and/or addition from the human neurotrypsin kringle domain of SEQ ID NO:6 and claim 3. They also disclose, cols. 13-18, preparation of expression vectors comprising a DNA encoding the human tPA and of host cells transformed with the expression vectors.

Claims 4, 6, 12 and 16 are rejected under 35 U.S.C. §102(e) as being anticipated by Elshourbagy et al., U.S. Patent No. 5,916,766, who disclose macrophage scavenger receptors of human and murine origin, SEQ ID NOs:2 and 7, DNA encoding the human receptor and, cols. 38-41, expression vectors and transformed host cells comprising the encoding DNA. The murine scavenger receptor cysteine-rich domain [SRCR], positions 394-489, shares 31% amino acid sequence similarity with the human neurotrypsin SRCR domain 1, amino acid positions 117-217, set forth in SEQ ID NO:6 herein, comprising extensive partial peptides that differ by "at least one" amino acid substitution, deletion, and/or addition from the human neurotrypsin SRCR domain 1 of claim 4.

Claims 4, 6, 12 and 16 are rejected under 35 U.S.C. §102(e) as being anticipated by Krieger et al., U.S. Patent No. 5,510,466, who disclose, Fig. 3, a bovine macrophage

scavenger receptor and DNA encoding the receptor. The bovine scavenger receptor cysteine-rich domain, positions 352-452, shares 58% amino acid sequence similarity with the human neurotrypsin SRCR domain 2, amino acid positions 227-327 of SEQ ID NO:6 herein, comprising extensive partial peptides differing from the human neurotrypsin SRCR domain 2 of claim 4 by "at least one" amino acid substitution, deletion, and/or addition. They also disclose, cols. 17 and 18, preparation of expression vectors and transformed host cells comprising a DNA encoding the receptor.

Claim 4, 6, 12 and 16 are rejected under 35 U.S.C. §102(e) as being anticipated by Krieger et al., U.S. Patent No. 5,624,904, who disclose another bovine macrophage scavenger receptor and DNA encoding the receptor, SEQ IDs NOs:2 and 1. This bovine receptor's SRCR domain, positions 350-449, shares 52% amino acid sequence similarity with the SRCR domain 3, amino acid positions 334-432 of human neurotrypsin set forth in SEQ ID NO:6 herein, comprising extensive partial peptides differing by "at least one" amino acid substitution, deletion, and/or addition from the SRCR domain 3 of human neurotrypsin of claim 4. They also disclose, cols. 12 and 13, preparation of expression vectors and transformed host cells comprising a DNA encoding the receptor.

Claim 4, 6, 12 and 16 are rejected under 35 U.S.C. §102(e) as being anticipated by Koths et al., U.S. Patent No. 5,624,904, who disclose a human macrophage scavenger receptor and DNA encoding the receptor, SEQ IDs NOs:10 and 9. The SRCR domain of this human receptor, positions 24-123, has 52% amino acid sequence similarity with the SRCR domain 4, amino acid positions 447-547 of human neurotrypsin set forth in SEQ ID NO:6 herein, comprising extensive partial peptides differing by "at least one" amino acid substitution, deletion, and/or addition from the human neurotrypsin SRCR domain 4 of claim 4. They also disclose, cols. 21 and 23, preparation of expression vectors and transformed host cells comprising a DNA encoding the receptor.

The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. §103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR §1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. §103(c) and potential 35 U.S.C. §§102(f) or (g) prior art under 35 U.S.C. §103(a).

Claims 7-9 and 11 are rejected under 35 U.S.C. §103(a) as being unpatentable over Sonderreger et al. in view of Au-Young et al.('637).

The disclosures of Sonderreger et al. of the cloning of a cDNA encoding a murine neurotrypsin, discussed hereinabove, are taken as before and their further disclosures are now cited of screening, see Fig. 7, for expression of the message encoding the protease in regions of the brain engaged in processing and storage of learned behaviors and memories, regions where, p. 216, tPA and uPA are also expressed and also are associated with learning processes. The disclosures of Au-Young et al. are also taken as before and their further teachings, cols. 8-11, of preparing expression vectors and transformed host cells comprising a human serine protease-encoding cDNA in order to practice a process for preparing the serine protease, are now cited as well as the teaching, col. 15 at lines 13-34, of using the recombinantly-produced serine protease in screening therapeutic compounds. It would have been obvious to one of ordinary skill in the art at the time the invention was made to insert the neurotrypsin-encoding DNA sequence of Sonderreger et al. into any of the various expression vectors of Au-Young et al. and to transform any of the various host cells of Au-Young et al. with the corresponding expression vector in order to practice a process for preparing the neurotrypsin, as well as practicing subsequent processes of using

the recombinantly-produced serine protease in screening therapeutic compounds. This is because such an artisan at that time would have had a reasonable expectation of success in recombinantly expressing the neurotrypsin using such expression vectors and transformed host cells in view of their common use for that purpose evidenced in the teachings of Au-Young et al. This is also because such an artisan at that time would have been motivated to recombinantly express the neurotrypsin in order to practice a process of screening therapeutic compounds where Sonderreger et al. teach that many well-known extracellular serine proteases common to all mammals are expressed in the nervous system of mammals and play critical roles in mediating neural plasticity, even in the brains of adult mammals.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to William W. Moore whose telephone number is (703) 308-0583. The examiner can be reached Monday through Friday from 9:00 AM to 5:30PM EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (703) 308-3804. Papers related to this application may be submitted to Group 1800 by facsimile transmission. The faxing of such papers must conform with the notice published November 15, 1989 in the Official Gazette, 1096 OG 30. Informal and unofficial communications may be sent to the Art Unit 1652 FAX number, (703) 308-0294. Official filings should be sent to the Technical Center 1600 FAX number which is (703) 308-4556.

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. §122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark Office on February 25, 1997 at 1195 OG 89. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

William W. Moore
August 30, 2000